Chromophobe renal cell carcinoma: current and controversial issues

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Abstract: It has been 35 years since Professor Thoenes and his colleagues discovered chromophobe renal cell carcinoma (RCC). Since then, our knowledge about this tumour entity has changed and novel tumour entities have been discovered. The aim of this review is to discuss recent molecular findings and open questions in diagnosing chromophobe-like/oncocytic neoplasms. The broader differential diagnosis of chromophobe-like and oncocytoma-like neoplasms includes SDH-deficient renal cell carcinoma, fumarate hydratase (FH) deficient RCC, epitheloid angiomyolipoma ('oncocytoma like'), MiT family translocation RCC and the emerging entity of eosinophilic solid and cystic renal cell carcinoma. After separation of these tumours from chromophobe RCC, it becomes evident that chromophobe RCC are low malignant tumours with a 5-6% risk of metastasis. Recent next generation sequencing (NGS) and DNA methylation profiling studies have confirmed Thoenes' theory of a distal tubule derived origin of chromophobe RCC and renal oncocytomas. Comprehensive genomic analyses of chromophobe RCC have demonstrated a low somatic mutation rate and identified TP53 and PTEN as the most frequently mutated genes, whereas 'unclassified' RCC with oncocytic or chromophobe-like features can show somatic inactivating mutations of TSC2 or activating mutations of MTOR as the primary molecular alterations. For the future, it would be desirable to create a category of 'oncocytic/chromophobe RCC, NOS' with the potential of further molecular studies for identification of TSC1/2 mutations in these rare tumours.

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GENITOURINARY PATHOLOGY

Chromophobe renal cell carcinoma: current and controversial issues

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Summary

It has been 35 years since Professor Thoenes and his colleagues discovered chromophobe renal cell carcinoma (RCC). Since then, our knowledge about this tumour entity has changed and novel tumour entities have been discovered. The aim of this review is to discuss recent molecular findings and open questions in diagnosing chromophobe-like/oncocytic neoplasms. The broader differential diagnosis of chromophobe-like and oncocytoma-like neoplasms includes SDH-deficient renal cell carcinoma, fumarate hydratase (FH) deficient RCC, epitheloid angiomyolipoma ('oncocytoma like'), MiT family translocation RCC and the emerging entity of eosinophilic solid and cystic renal cell carcinoma. After separation of these tumours from chromophobe RCC, it becomes evident that chromophobe RCC are low malignant tumours with a 5–6% risk of metastasis. Recent next generation sequencing (NGS) and DNA methylation profiling studies have confirmed Thoenes' theory of a distal tubule derived origin of chromophobe RCC and renal oncocytomas. Comprehensive genomic analyses of chromophobe RCC have demonstrated a low somatic mutation rate and identified *TP53* and *PTEN* as the most frequently mutated genes, whereas 'unclassified' RCC with oncocytic or chromophobe-like features can show somatic inactivating mutations of *TSC2* or activating mutations of *MTOR* as the primary molecular alterations. For the future, it would be desirable to create a category of 'oncocytic/chromophobe RCC, NOS' with the potential of further molecular studies for identification of *TSC1/2* mutations in these rare tumours.

Key words: Molecular pathology; classification; differential diagnosis; immunohistochemistry; history.

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RECOGNITION OF CHROMOPHOBE RENAL CELL CARCINOMA

In the 1975 United States Armed Forces Institute of Pathology (AFIP) Atlas of Tumour Pathology[1] and the 1981 World Health Organization (WHO) classification,[2] renal cell carcinoma (RCC) was mainly diagnosed as 'renal adenocarcinoma', but it was evident that histological subtyping was of prognostic significance.[3] Classification attempts before 1950 included subtypes according to the predominant cytoplasmic or architectural features with clear cell carcinomas, papillary carcinomas and granular cell carcinomas.[4] Renal tumours that were composed of 'oncocytes' had been already described in 1942. This name came from the dominant cell type of large, eosinophilic cells with granular cytoplasm. Later, oncocytoma was accepted as a benign renal tumour entity, but there were already descriptions of malignant forms of oncocytomas, which were probably chromophobe RCC.[3,5] In 1985 and 1988, Thoenes *et al.* reported on RCCs composed of 'chromophobe' cells.[6,7] This designation resulted from an observation of Bannasch *et al.* in 1974 in nitrosomorpholine-induced renal neoplasia in rats.[8] These tumours in rats showed a peculiar histomorphology; by light microscopy, 'chromophobe' cells had a slightly opaque finely reticular cytoplasm when stained with haematoxylin and eosin. In the 1980s, classification proposals for human RCC used characteristic cellular features for their entities. With the recognition of a 'chromophobe' RCC subtype, Thoenes *et al.* proposed in 1986 the Mainz classification system (Fig. 1) with tumour subtypes classified consequently on the basis of predominant cytoplasmic staining characteristics.[9] They separated clear cell carcinoma from chromophilic carcinoma and chromophobe RCCs, and added Bellini duct carcinoma on the basis of the 'cell of origin' concept. Cells of chromophobe RCC were distinguished from the clear cells of clear cell carcinoma and eosinophilic cells of 'chromophilic' papillary carcinoma. In contrast to oncocytoma, chromophobe RCC showed a strong positive reaction of their cytoplasm with Hale's colloidal iron method. In the following years, the Mainz classification was validated by cytogenetic studies, mainly performed by Kovacs.[10–12] Most importantly, chromophobe RCC was characterised by a unique genetic background with loss of heterozygosity 1, 2, 6, 10, 13, 17, 21 and hypodiploidy on flow cytometry studies in addition to its typical histological appearance.[13] At the 1997 Heidelberg conference, the molecular background of different renal cancer subtypes was introduced into a classification system.[14] As a result of the Heidelberg/Rochester consensus conferences, the 1998 WHO classification gave chromophobe RCC its own entity, 12 years after the Mainz classification.[15] The 2004 and 2016 WHO classifications define chromophobe RCC as the third most common subtype of RCC.[16,17]

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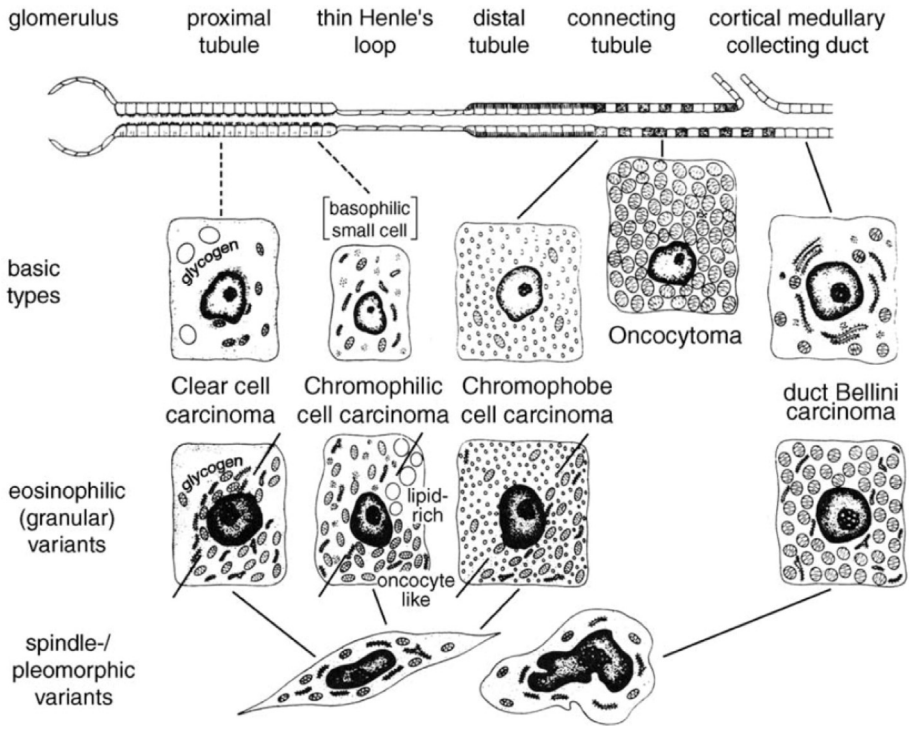

Fig. 1 Mainz Classification with a scheme of the various nephron/collecting duct segments and their different phenotypical relation to the classified epithelial renal cell tumours.[3]

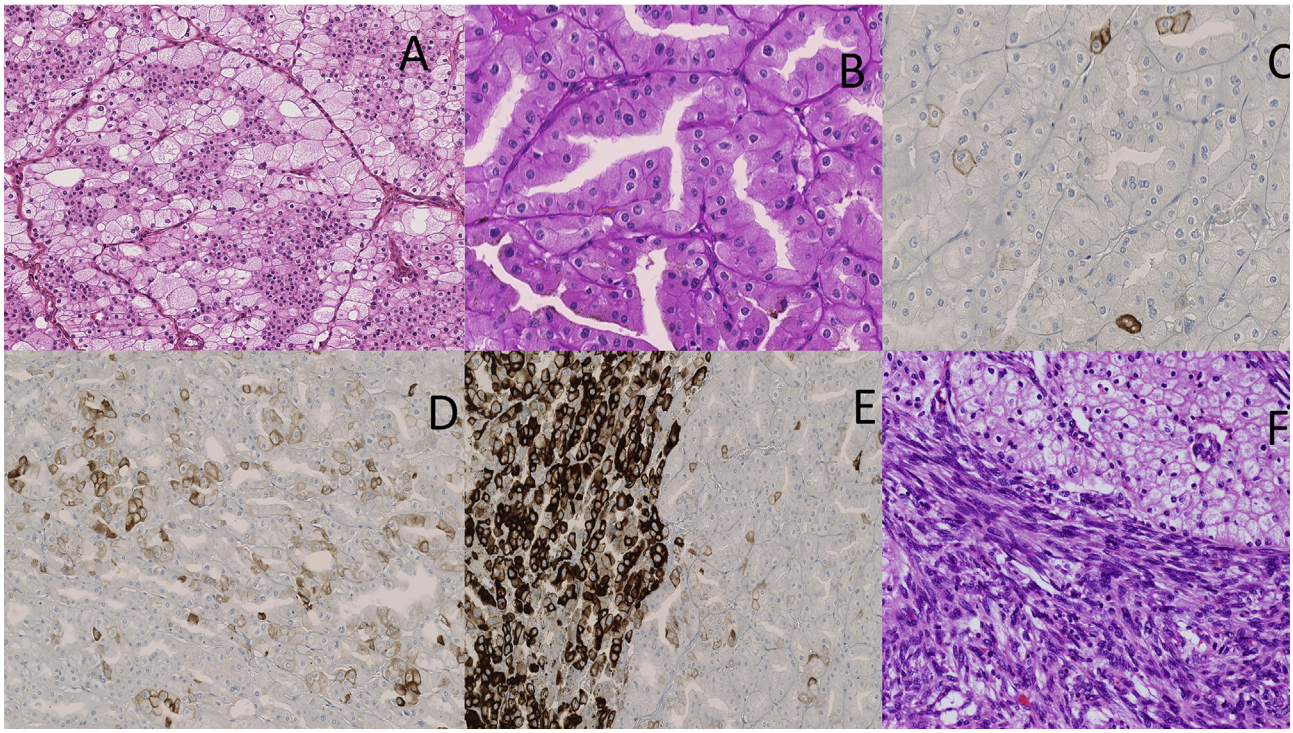

Fig. 2 Morphological heterogeneity of chromophobe renal cell carcinoma (RCC). (A) Chromophobe RCC consisting of both cell types, eosinophilic and pale cells. (B–E) Intratumoural heterogeneity of CK7 staining in chromophobe RCC. (B) Tumour area almost purely composed of eosinophilic cells. Note perinuclear halos. (C) Tumour area with CK7 positivity in single cells, similar to oncocytomas. Note bi-nucleated tumour cells. (D) Tumour area with groups of CK7-positive cells, typical for chromophobe RCC. (E) Tumour area with diffuse and strong CK7 staining. (F) Chromophobe RCC with sarcomatoid differentiation.

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EPIDEMIOLOGY, MACROSCOPY, HISTOPATHOLOGY

Since the first description by Thoenes *et al.*, epidemiology and pathological features of chromophobe RCC have been extensively studied.[18–23] Chromophobe RCC accounts for approximately 5–7% of RCC. Most tumours are sporadic. Birt–Hogg–Dubé (BHD) syndrome, an autosomal dominant disorder associated with mutation in the *Folliculin* gene,[24] and Cowden syndrome with germline mutations in *PTEN* are associated with a higher incidence of chromophobe-like or oncocytoma-like neoplasms.

Chromophobe RCC are characteristically well circumscribed but not encapsulated. Whereas most oncocytoma have a brown or mahagony colour, the cut surface of classic chromophobe RCC is grey or light tan. Histologically, they grow predominantly in solid sheets, separated by vascular septs (Fig. 2A,B). Some tumours show variable nested, trabecular, alveolar, microcystic or even papillary patterns.[25] A small percentage exhibits sarcomatoid growth[26] (Fig. 2F). Classic tumours show predominance of pale cells with clear cytoplasm. The cytoplasm is translucent and finely reticulated, sometimes microvesiculated. Some larger cells with more voluminous clear to foamy ('hydropic') cytoplasm are often present among pale cells. Another cell type is characterised by densely eosinophilic or granular cytoplasm (Fig. 2B). Pale and eosinophilic cell types can be mixed (Fig. 2A). Hyperchromatic nuclei with irregular, wrinkled outlines ('raisinoid') are most characteristic. Another characteristic feature is presence of perinuclear cytoplasmic clarity (so called perinuclear halos). Binucleated cells are present in virtually all cases. Cell membranes usually appear prominent ('plant cell-like'), an important criterion compared to oncocytoma. Hyperchromatic bizarre nuclear atypia similar to those in renal oncocytoma can be common. The prevalence of sarcomatoid differentiation ranges from 1.8% to 8.8%.[27,28] Mitotic activity is very uncommon in chromophobe RCC. Since the first description of chromophobe RCC, the differential diagnosis between renal oncocytoma and chromophobe RCC remains difficult in some cases. A recent survey among urological pathologists regarding oncocytic tumours showed that most pathologists used immunohistochemistry for this separation.[29] More than one mitotic figure was regarded as incompatible with oncocytoma diagnosis by many uropathologists. Minor areas with nuclear wrinkling, focal perinuclear clearing, and multinucleation did not necessarily exclude oncocytoma.

ELECTRON MICROSCOPY, HISTOCHEMISTRY, AND IMMUNOHISTOCHEMISTRY

For many years, electron microscopy was used to diagnose oncocytomas and chromophobe RCC. Thoenes *et al.* reported on vesicular structures possibly derived from the endoplasmic reticulum or from mitochondria chromophobe RCC and oncocytomas.[7,9] Several ultrastructural studies have shown that the typical cells of chromophobe RCC ('pale cells') are characterised by numerous cytoplasmic microvesicles, a feature probably related to defective mitochondrial development. In more eosinophilic cells of chromophobe RCC, mitochondria are very abundant.[2,6–30] Thoenes *et al.* also used colloidal (Hale's) iron staining, demonstrating a variable granular or reticular and diffuse cytoplasmic staining in most chromophobe RCC in contrast to oncocytomas.[7] However, colloidal (Hale's) iron staining is nowadays less popular, because some chromophobe RCC show only focal or weak or even luminal-type staining.[29] Immunohistochemically, CK7 is a very important marker, showing diffuse expression in more than 75% of chromophobe RCC[31] (Fig. 2C–E). Occasionally, there are only a few clusters of weak cells with membranous accentuation. Such CK7-positive cell clusters should not be present in oncocytomas, but CK7-positive cells can be present around the central scar of an oncocytoma. CD117 and Ksp-Cadherin are diffusely positive in the overwhelming majority of chromophobe RCCs. Most cases also show positivity with MOP-31, Claudin-7 and EpCAM (BerEP4).[32] CA9 is negative and also CD10 is usually negative but may show focal positivity.[33] Rare CK7-positive cells ($\leq$5% as single cells, not clusters) are regarded as most supportive of oncocytoma.[29]

MOLECULAR STUDIES AND THE 'CELL OF ORIGIN' THEORY

Thoenes assumed that chromophobe RCC had a different histogenetic derivation than clear cell and other RCCs.[34–36] On the basis of a different histology and immunoprofile, he argued that chromophobe renal cancer and oncocytoma were derived from the intercalated cells of the distal tubules in the renal cortex (Fig. 1). This concept is still controversial, because the cancer stem cell theory with tumourigenic stem cells rather than terminally differentiated tubular cells is also relevant for many RCC subtypes.[37,38] Interestingly, a recent next generation sequencing (NGS) analysis identified FOXI1, RHCG, and LINC01187 in classic and eosinophilic chromophobe RCCs, as well as metastatic chromophobe RCC.[39] These biomarkers are also expressed in other oncocytic renal neoplasms, including unclassified RCC with oncocytic features, hybrid oncocytic and chromophobe tumours, and oncocytomas, but not in other renal tumour subtypes. FOXI1 is an essential transcription factor for differentiation of distal tubule intercalated cells. This finding is somehow in line with Thoenes' 'cell of origin' theory for oncocytic renal tumours. Recent DNA methylation profiling and single cell sequencing studies have identified chromophobe RCC specific methylation with similarities to distal tubule methylation patterns.[40,41]

Various cytogenetic, comparative genomic hybridisation and recent molecular and proteome studies have confirmed the very unique and characteristic genotype, with multiple chromosomal losses of chromosomes 1, 2, 6, 10, 13, 17, 21 and sex chromosome in the majority of chromophobe RCCs.[13,42,43] Genomic instability, including whole chromosome aneuploidy, is a hallmark of human cancer. Given the level of chromosomal losses in chromophobe RCC, tumour growth must be the consequence of a special molecular pathway. The phenomenon of tumour cell growth in spite of multiple chromosomal losses can be potentially explained by involvement of *CYCLOPS* (Copy number alterations Yielding Cancer Liabilities Owing to Partial losS) genes. *CYCLOPS* genes receive little feedback regulation in their expression when altered by somatic copy number alterations. Splicing factor 3B subunit 1 (SF3B1) belongs to this group of *CYCLOPS* genes and has been recently identified as a potential novel, non-driver cancer gene in chromophobe RCC.[44]

Given an accumulation of mitochondria in chromophobe RCC and oncocytoma, it is tempting to search for alterations

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in mtDNA. Indeed, some studies have disclosed frequent somatic mtDNA mutations in oncocytoma and chromophobe RCC,[45–47] but mtDNA mutations are not specific for chromophobe RCC.[48]

Comprehensive genomic analyses of chromophobe RCC cohorts demonstrated a low somatic mutation rate in chromophobe RCC and identified *TP53* and *PTEN* as the most frequently mutated genes.[48–51] Mutation rates of *TP53* and *PTEN* were higher in chromophobe RCC patients with metastatic disease[52] and with sarcomatoid features.

CDKN1A, which resides in 6p21.2, is affected by frequent loss of one chromosome 6 allele in chromophobe RCC.[53] Analysis of TCGA data of chromophobe RCC demonstrated that loss of one *CDKN1A* allele was closely linked to lower *CDKN1A* mRNA expression levels. It has been recently shown that decreased CDKN1A expression at mRNA and protein levels were associated with short overall survival and were independent predictors of prognosis in chromophobe RCC.

Other NGS analyses as well as the combination of gene expression and proteome profiles, high throughput SNP genotyping, and pathway analysis have been used to distinguish chromophobe RCC from oncocytoma and confirm dysregulated pathways of c-erbB2 and mammalian target of rapamycin (mTOR) signalling in chromophobe RCC.[39,50,54–57]

ARE THERE SUBTYPES OF CHROMOPHOBE RCC?

Eosinophilic subtype

Thoenes *et al.* used the term 'chromophobe cell' for larger cells with reticular, but not clear cytoplasm and prominent cell membranes ('plant cell-like').[7] Three years later, these authors described eosinophilic cells with smaller size and with fine oxyphilic granularity as a second cell component of chromophobe RCC.[6] Crotty *et al.* used the term 'pale cell' instead of the formerly used term 'chromophobe cell', and considered 'pale cell' and 'eosinophilic cell' as two main cell types in chromophobe RCC.[18] Most chromophobe RCCs consist of both cell types, which are typically mixed, with eosinophilic cells usually arranged at the centre and pale cells usually arranged at the periphery of the sheets or nests. The current 2016 WHO classification states that eosinophilic chromophobe RCC 'is almost purely composed of eosinophilic cells' and that 'the majority of cells should be eosinophilic cells',[17] but there is currently a lack of exact criteria to clearly define the eosinophilic subtype of chromophobe RCC. As a consequence of this lack of stringent criteria for subtyping chromophobe RCC, distribution of chromophobe RCC variants varies extremely between different studies and it is difficult to demonstrate molecular differences between both groups.[58,59] Ohashi *et al.* have recently shown that there is no difference in the prognosis of 'classic' and 'eosinophilic' chromophobe RCC.[58] Therefore, the value of reporting the eosinophilic variant of chromophobe RCC is to remind people that they can be mistaken for oncocytomas.

Hybrid oncocytic and chromophobe tumours

Some chromophobe tumours demonstrating nuclear pleomorphism and mitotic index beyond that acceptable for oncocytoma were initially described in patients with BHD syndrome. By conventional pathological examination, hybrid oncocytic and chromophobe tumours harbour a mixture of cells with morphological and immunophenotypical features that overlap with those of renal oncocytoma and chromophobe RCC. Therefore, the term 'hybrid oncocytic and chromophobe tumour' was proposed[20] and is now variably used in several scenarios, including tumours in BHD syndrome, oncocytomatosis and for sporadic cases.[60–62] Unfortunately, the morphological criteria are not exactly defined. Some hybrid oncocytic and chromophobe tumours show a mosaic pattern with defined renal oncocytoma-like zones with solid nests/alveoli in close contact to chromophobe RCC-like zones (Fig. 2), whereas others show an ambiguous morphology with oncocytoma-like architecture, but absence of nuclear wrinkling and perinuclear halos as seen in the extent of chromophobe RCC.

The 2016 WHO classification includes a statement that a small subset of tumours have overlapping histology between oncocytoma and chromophobe RCC and recommends that such tumours should be designated as hybrid oncocytic and chromophobe tumour. There is evidence that the metastatic rate of hybrid oncocytic and chromophobe tumours ranges between 2% in a sporadic setting[20,60,63–67] and 5% in a BHD syndrome setting.[68,69] This is comparable to chromophobe RCC with a low metastatic rate of <10%. The designation of hybrid oncocytic and chromophobe tumour as its own tumour category is controversial, with authors suggesting that hybrid oncocytic and chromophobe tumours represent a variant of classic renal oncocytoma and others as variant of the eosinophilic variant of chromophobe RCC.[60,61] A very recent and comprehensive study by Ruiz-Cordero *et al.* studied hybrid oncocytic and chromophobe tumour by gene expression profiling and targeted NGS and compared the results with chromophobe RCC and renal oncocytoma.[62] Hybrid oncocytic and chromophobe tumours were more frequently multifocal and did not exhibit mutations in genes that are recurrently mutated in renal oncocytoma or chromophobe RCC, but they showed copy number alterations primarily involving losses in chromosomes 1 and X/Y. mRNA transcript data separated hybrid oncocytic and chromophobe tumour from renal oncocytoma and chromophobe RCC. Based on these results, the authors concluded that hybrid oncocytic and chromophobe tumour represents a renal tumour variant that is intermediate between renal oncocytoma and chromophobe RCC.

A recent survey among uropathologists revealed that for tumours with mixed or inconclusive features, many participants use an intermediate diagnostic category that does not label the tumour as unequivocally benign or malignant, typically 'oncocytic neoplasm' or 'tumour' with comment.[29] Therefore, most participants at the International Society of Urological Pathology (ISUP) conference indicated that they view hybrid oncocytic and chromophobe tumour as a subset of chromophobe RCC.[70] Overlapping histology between oncocytoma and chromophobe RCC reflects intratumoural heterogeneity of chromophobe RCC rather than its own subtype.

Is oncocytoma a precursor lesion of chromophobe RCC?

Thoenes *et al.* argued that there are no precursor lesions of chromophobe RCC. Given the similarity of the eosinophilic

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variant of chromophobe RCC and oncocytoma, one might hypothesise that oncocytoma represents the benign counterpart of chromophobe RCC. In a recent study, almost all eosinophilic and all classic chromophobe RCC revealed chromosome 1 loss, suggesting that this may be an early event in chromophobe RCC tumourigenesis. The only molecular alteration shared by chromophobe RCC and renal oncocytoma is loss of chromosome 1,[58,71–73] consistent with a speculation by Tan *et al.* that this may represent an early event in neoplastic transformation of a common progenitor cell in both chromophobe RCC and renal oncocytoma.[54] In oncocytomas, chromosome 1 loss may precede other molecular events leading to malignancy in lesions that progress to chromophobe RCC. This situation is comparable to chromosome 3p loss in clear cell RCC, which is thought to be an early event in carcinogenesis of ccRCC.

CHROMOPHOBE-LIKE AND ONCOCYTOMA-LIKE NEOPLASMS: RECENT DEVELOPMENTS IN CLASSIFICATION

Differential diagnosis

During the last decade, unequivocal recognition of chromophobe RCC with a typical histology and immunophenotype has allowed the separation of other renal tumour entities with oncocytoma/chromophobe-like histomorphology. The most important differential diagnosis is SDH-deficient RCC,[74,75] a tumour entity very similar to chromophobe RCC. It is important to recognise these tumours because they represent a hereditary tumour entity. The broader differential diagnosis of chromophobe-like and oncocytoma-like neoplasms may now include tumours occurring in patients with BHD syndrome, fumarate hydratase (FH)-deficient RCC, epitheloid angiomyolipoma ('oncocytoma-like'), MiT family (TFE3 or TFEB) translocation RCC and the emerging entity of eosinophilic solid and cystic (ESC) RCC with a characteristic CK20 expression.

Tumours with TSC alterations

Most importantly, recent studies have identified many tumours with eosinophilic cytoplasm and oncocytic or chromophobe-like features in the group of 'unclassified' RCC. Li *et al.* reviewed 33 unclassified RCCs with predominantly eosinophilic cytoplasm in patients aged 35 years or younger.[76] They identified SDHB-deficient, FH-deficient and ESC cases, but 33% remained 'unclassified'. Perrino *et al.* analysed 136 unclassified RCC and assigned them to the following morphological groups: predominantly oncocytoma/chromophobe RCC-like; clear cell RCC-like; papillary RCC-like; collecting duct-like; and pure sarcomatoid differentiation.[77] The majority (73%) was predominantly renal oncocytoma-like/chromophobe RCC-like phenotype. Interestingly, different groups have very recently analysed 'unclassified' RCC with chromophobe-like or renal oncocytoma-like RCC and with eosinophilic or vacuolated cytoplasm by targeted NGS. Although the morphology of these cases was very close to renal oncocytoma or the eosinophilic variant of chromophobe RCC, these tumours ended up in the 'unclassified' RCC category because of an unusual histology or immunophenotype with a dense and more abundant eosinophilic cytoplasm, diffuse staining of CK7, absent to weak staining of CK20 or positivity for P504S.[78,79] Chen *et al.* studied five cases and Tjota *et al.* 18 cases. Both groups identified somatic inactivating mutations of *TSC2* or activating mutations of *MTOR* as the primary molecular alterations, consistent with hyperactive mTOR complex 1 (mTORC1) signalling in most chromophobe-like or renal oncocytoma-like cases.

ESC RCC with CK20 expression can also show TSC gene mutations or biallelic losses.[80] Interestingly, some ESC RCC have solid areas with chromophobe-like appearance.[81] Moreover, ESC tumours have recently been described as a sporadic form of RCC with histological similarity to a subset of renal tumours encountered in TSC patients. Some authors argue that somatic mutations of *TSC2* or *MTOR* characterise a morphologically distinct subset of sporadic RCC with eosinophilic and vacuolated cytoplasm. However, TSC/MTOR associated neoplasms are a morphologically and immunohistochemically heterogeneous group. TSC/MTOR associated neoplasms include eosinophilic renal tumours with a chromophobe-like appearance with perinuclear halos. Some of these tumours are diffusely positive for CK7 but negative (or only focally positive) for CK20. Trpkov *et al.* proposed the term 'low grade oncocytic tumours' (LOT) with CD117 negativity and CK7 positivity as an emerging renal tumour entity with indolent clinical behaviour,[82] but further studies are warranted to prove that LOT really represents a distinct type of tumour. For the time being, they should be regarded as variant of unclassified 'chromophobe-like' RCC. So-called RCC 'with prominent leiomyomatous stroma' also frequently harbour *TSC1/TSC2*, *MTOR*, and/or *ELOC* (*TCEB1*) mutations, consistent with hyperactive mTOR complex.[83] These tumours can have some morphological overlap with ccRCC and clear cell papillary RCC, supporting the hypothesis that previously published *TCEB1* (*ELOC*) mutated RCCs are identical, and indistinguishable from a subset of hereditary TSC associated RCCs, originally described as 'RAT-like' or 'TSC associated papillary type.'

In summary, it would be desirable to create a new category of 'oncocytic/chromophobe RCC, NOS'. The main advantage for creating this category is the potential of further molecular studies for identification of *TSC1/2* mutations. According to recently published data, such tumours have a good prognosis, but identification of TSC mutations by NGS could suggest a treatment by mTOR inhibitors. In contrast, a category of *TSC1/2* mutated RCC would encompass a category of tumours with an extremely broad histological spectrum, which is only molecularly defined and cannot be diagnosed by histology alone.

PROGNOSIS AND GRADING OF CHROMOPHOBE RCC

Thoenes *et al.* had already argued that chromophobe RCC may have a better prognosis than clear cell RCC, but his series of 13 and 33 tumours were too small to prove this hypothesis.[6,7] Meanwhile several large studies have indicated that prognosis of chromophobe RCC is much better than that of clear cell RCC and papillary RCC. Most chromophobe RCC have a favourable outcome and low risk of metastasis, but there is evidence that chromophobe RCC have a predisposition to metastasise into the liver.[84] Ten year overall survival rates of between 80 and 90% have been reported.[20,22,85,86] It is important to note that tumour specific survival or time to tumour progression are much more

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important than overall survival measures, because death of disease occurs only in about 5–6% of patients with chromophobe RCC.[26] Clinically, it would be extremely helpful to identify this small subgroup at increased risk for metastasis.

Numerous studies have confirmed that tumour size and the presence of sarcomatoid morphology indicates poor prognosis and increased risk of metastatic development for chromophobe RCC.[23,28,85–88] Tumour grade is also important, but the four tiered nuclear grading system proposed by ISUP could not be validated for chromophobe RCC, because they have an innate constitutive atypia including prominent nucleoli, nuclear irregularities and bi-nucleation.[89] In the past, there have been several attempts to develop a grading system for chromophobe RCC,[20–22,27,85,86,90,91] considering the inherent geographic nuclear crowding and presence of anaplasia. Paner *et al.* suggested a three tiered chromophobe tumour grading scheme and supplemented nuclear grading with additional variables including geographic nuclear crowding and objective nuclear size.[86] With this approach, the majority of chromophobe RCCs are of a lower grade, but there is inter- and intra-observer variability in the identification of nuclear crowding and nuclear pleomorphism. Lohse *et al.* applied a four tiered standardised grading for chromophobe RCC and demonstrated a significant overlap in grades 3, 2 and 1 chromophobe RCC.[92]

Recently, a two tiered grading system (low vs high grade) was proposed by Ohashi *et al.*, using sarcomatoid differentiation and presence of tumour necrosis as parameters.[26] The advantages of this two tiered grading system over previous proposals of three or four tiered grading systems, are a high to very high concordance between different pathologists, and a high reliability in identification of patients with increased risk of chromophobe RCC progression. Metastasis of low grade tumours was absent in four different cohorts from Japan, Germany, Switzerland and Italy.

TREATMENT OF METASTATIC CHROMOPHOBE RCC

Patients with high grade tumours (sarcomatoid differentiation and/or tumour necrosis) should have a stringent follow-up because of their increased risk of metastasis.[23] Because metastasis of chromophobe RCC is very rare, dedicated prospective clinical trials for metastatic chromophobe RCC are not available and patients are treated as non-clear cell RCC. Favourable responses to VGF-tyrosine kinase inhibitor agent, mTOR inhibitors and immune checkpoint inhibitors have been reported. Sarcomatoid differentiation in chromophobe RCC is an indicator of limited response to systemic therapy and poor overall survival.[28] However, the immunological landscape of renal tumour with sarcomatoid areas shows a different molecular background with frequent expression of programed cell death ligand-1 (PD-L1) and high levels of tumour infiltrating lymphocytes.[93,94] These determinants explain the activity of immune checkpoint inhibitors in RCC with sarcomatoid differentiation. This has been confirmed by retrospective studies and subgroup analyses of large randomised phase 3 trials.

Therefore, immune checkpoint inhibitor combinations could also be relevant in patients with metastatic chromophobe RCC with sarcomatoid differentiation.[95,96] Patients with metastatic chromophobe RCC might be considered for targeted NGS testing. If there is a molecular mutation, appropriate molecular targeted therapy can be provided. This is particularly critical for TSC associated 'chromophobe-like' RCCs as there are mTOR inhibitors currently available for the treatment of RCCs.[97] A few case reports have demonstrated clinical benefit in using mTOR inhibitors to treat TSC associated RCCs, including complete response in a case of sporadic, metastatic ESC RCC.[78,98] Interestingly, one of the cases described as responding to mTOR inhibitor therapy was originally diagnosed as chromophobe RCC. The patient was found to have a germline *TSC1* mutation without other characteristics of a TSC tumour.[99]

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